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14. ABSTRACT

The complex of multiple symptoms known as Gulf War Illness (GWI) continues to affect a substantial number of veterans who served in the 1990-1991 Gulf War. Despite considerable research, the biological processes underlying veterans' symptoms have not been clearly elucidated. In order to develop useful diagnostic tests and optimize the search for effective GWI treatments, it is imperative to establish a more definitive and integrated understanding of the pathophysiology of this problem. This study utilizes a case-control design to evaluate diverse biological measures in a single, well-characterized and population-based sample of 130 Gulf War veterans residing in Texas. Eighty veterans with GWI are compared to 50 healthy veteran controls in a protocol that includes physical and neuropsychological evaluations, neuroimaging (MRI, fMRI, DTI), adrenal function tests, and diverse immune, inflammatory, and coagulation measures. Statistical analyses will determine which objective measures significantly distinguish GWI cases from controls, and explore the extent to which biological findings are interrelated and are associated with identifiable veteran subgroups. When complete, the study is expected to clarify many of the ambiguities currently associated with GWI and improve understanding of the biological processes that underlie veterans' symptoms. This will facilitate efforts to identify useful diagnostic tests and promising treatments.

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Assessment of Diverse Biological Indicators in Gulf War Illness:
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Introduction

At least one in four military veterans who served in the 1990-1991 Persian Gulf War continue to suffer from a serious, often debilitating illness that is not explained by established medical or psychiatric diagnoses. This symptomatic illness is commonly known as Gulf War illness (GWI), and is characterized by a profile of concurrent symptoms that typically includes persistent headaches, memory and cognitive difficulties, widespread pain, unexplained fatigue, gastrointestinal problems, and other difficulties. Studies consistently indicate that GWI is not a psychiatric disorder and is not the result of combat stress (Institute of Medicine 2010; Research Advisory Committee on Gulf War Veterans' Illnesses (RAC) 2008). Longitudinal studies indicate that few veterans who developed GWI during and after the 1991 Gulf War have recovered, or even substantially improved, with time (RAC 2008, Wolfe 2002, Kang 2008, Hotopf 2003).

Despite considerable research related to GWI, the pathophysiological underpinnings of veterans' symptoms have not yet been clearly elucidated. Studies have identified diverse biological differences between groups of GWI cases and healthy controls associated with neurological, endocrine, immune, and hematological measures. Most results, however, have been "one-off" findings. That is, most objective findings related to GWI have come from individual studies that have evaluated different questions, sometimes with limited samples or methodologies. Even studies evaluating abnormalities in the same biological system have used diverse methods and outcome measures, making comparison of results difficult or impossible. There are relatively few examples of specific GWI-related biological findings that have been replicated by a second team of investigators. There are also few instances in which measures related to different biological systems, for example, measures of brain function and immune function, have been evaluated in a single group of Gulf War veterans. It is therefore not possible to know whether findings in different biological systems occur in the same individuals, or in discrete subsets of ill veterans. And for many of the biological differences identified thus far, there is no clear rationale to explain why or how they relate to symptoms characteristic of GWI.

As a result, a relatively large body of suggestive evidence has accumulated that provides preliminary indications of biological processes that underlie veterans' symptoms. But the lack of replicated findings, the difficulty of comparing results from different groups, and the lack of information about the co-occurrence of findings in different systems presents an enormous barrier to developing a clear understanding of the biological nature of GWI. This limited understanding has slowed efforts to identify promising avenues for diagnostic tests and treatments.

The present study utilizes a case-control design to evaluate diverse biological measures in a well-characterized sample of 130 veterans, recruited from among 1991 Gulf War veterans who currently reside in Central Texas. Eighty veterans with GWI, defined by Kansas GWI criteria (Steele 2000), are compared to 50 healthy Gulf War veteran controls in a protocol that includes physical examinations, neuroimaging (MRI volumetric assessments, fMRI, diffusion tensor imaging), neuropsychological evaluations, assessment of hypothalamic-pituitary-adrenal function, standard diagnostic laboratory tests, and blood tests to evaluate immune, inflammatory,

and coagulation parameters. Statistical analyses will determine which measures significantly distinguish GWI cases from controls, and will explore the extent to which findings are interrelated and/or are associated with subgroups of ill veterans distinguished by biological measures, deployment experiences/exposures, or illness severity and characteristics.

This multidisciplinary study was designed as a collaborative project between investigators at Baylor University, the Scott & White Healthcare System, Texas A&M Health Science Center, Columbia University School of Public Health, and the Minneapolis (MN) VA Medical Center. Veterans are evaluated over two consecutive mornings using a protocol designed to address multiple questions at once in the most rigorous, comprehensive, and efficient way possible. The study protocol emphasizes the use of testing methods that, if found to successfully distinguish sick from healthy veterans, can most readily be developed for clinical application in the near term.

In the current year of the project, we have continued to experience extended delays in project start-up associated with developments at both our partnering institutions and with offices in the Department of Defense, as detailed in this report. As a result, we have requested a one year extension without funds (EWOF). In order to implement the project in a timely way, we have also determined it necessary to relocate the PI's research program to another institution, where availability of additional research resources will allow us to accelerate study progress and completion.

Body

Task 1. Prepare and Submit Documents to Obtain Regulatory Approvals

This project is obtaining data from human subjects, and was designed to include research activities conducted at five institutions. This includes two primary institutions (Baylor University and Scott & White Healthcare) where investigators will interact directly with human subjects to obtain data and blood samples. It also includes three secondary sites (Texas A&M Health Science Center, Columbia School of Public Health, and Minneapolis VA Medical Center), where research activities are limited to processing coded blood samples obtained at the primary sites. This multi-institutional project has therefore required human subjects' determinations from five Institutional Review Boards (IRBs) and the Army's Office of Human Research Protections (HRPO).

The majority of activities accomplished to date relate to the somewhat complex regulatory issues and processes associated with the project. This has included Office of Management and Budget (OMB) submissions to the Army and DOD information management offices, and human subjects' submissions to all five IRBs and to HRPO. The regulatory process has also included resubmissions and additional reviews as needed at each institution to address changes requested by partnering IRBs, changes made to the study protocol, changes requested by HRPO, and annual continuing review after initial human subjects' approvals. All human subjects' regulatory approvals are current at this time.

Federal Office of Management and Budget (OMB) Submissions
We initially understood, based on information provided by several offices within the Department of Defense (DOD), that our study required review and approval by the federal Office of Management and Budget (OMB) under the federal Paperwork Reduction Act (PRA). We were advised that our data collection would need OMB approval in order for DOD's Defense Manpower Data Center (DMDC) to provide the project with names of Gulf War veterans residing in our target area in Texas. These names were needed to identify and recruit the "gold standard" population-based sample required for the project. We had been informed by the DOD office that handles Army OMB submissions that the OMB approval process typically requires eight months. Baylor provided the required PRA documentation to the Army for submission to OMB in June 2012. We were informed in December 2012, however, that the documents were never forwarded to OMB by the Army and DOD offices responsible for handling OMB submissions. After a series of requests and discussions with both Army and DOD information offices, we received confirmation, early in 2013, that the project was not subject to the federal PRA and could proceed without OMB approval once all required human subjects' approvals were in place.

Human Subjects' Approvals
After obtaining initial IRB approvals from our two primary sites (Baylor and Scott & White), human subjects' documents were submitted to the Army's Office of Human Research Protections (HRPO) in November, 2012. Changes requested by HRPO in March, 2013, were easily

addressed, but our revised documents were not resubmitted to HRPO until September 30, 2013, due to delays resulting from (1) the need to move the MRI scanning component of the study from the original intended site (the mobile MRI facility at VA's Center of Excellence for Returning War Veterans in Temple, TX) to Scott &White, and (2) additional Scott & White-requested changes to the study protocol and Informed Consent documents that posed a potentially serious problem for maintaining the privacy of human subjects. After extended discussions and meetings, Scott & White's legal office modified their request, limiting the circumstances in which research data would be entered into the hospital's electronic medical record (EMR) system. Still, it was necessary to submit information associated with the MRI site change as well as the protocol/informed consent changes associated with use of the EMR as IRB amendments to Baylor and Scott & White prior to sending all changes to Army HRPO for review and approval. Final Army HRPO approvals, for the both Baylor and Scott & White sites, were obtained on November 26, 2013.

Upon receiving HRPO approvals, we submitted our data request to DMDC in December, 2013, to obtain sampling information on 1991 Gulf War veterans residing in Central Texas. The data request was approved by the DMDC human subjects' office and by the DMDC Survey Division. However, as detailed below, extended delays followed and we have not yet obtained the DMDC data needed to develop the study sample and initiate subject recruitment and data collection.

While continuing to work to identify solutions to address the challenges raised in obtaining DMDC data, we also developed an alternate plan for subject recruitment. The alternate approach was approved by our CDMRP Science Officer in late August 2014 and subsequently approved by both Baylor and Scott & White IRBs and Army HRPO. Annual IRB continuing review approvals have subsequently been obtained from both institutions and submitted to the HRPO Continuing Review office.

Research activities at the three secondary sites for the project (Columbia School of Public Health, Minneapolis VAMC, and Texas A&M Health Science Center) are limited to analyses of coded blood samples that Baylor will provide to laboratories at each site. The IRBs at all three secondary sites have designated the research activities conducted at their institutions for the project to be exempt from human subjects' review.

Task 2. Identify and Interview Sample of Gulf War era Veterans for Study Participation

Task 2 previously included development and recruitment of a population-based sample of Gulf War veterans but was recently modified, under the revised statement of work, to allow recruitment of the study sample using a less rigorous approach. The project was originally designed to provide a more definitive elucidation of the diverse pathobiological processes associated with GWI. This was to be accomplished by determining the degree to which a number of biological alterations thought to underlie the symptoms of GWI could be identified and/or replicated in a single, rigorously-identified sample of Gulf War veterans. An important aspect of the original design was the use of a "gold standard" population-based sample of Gulf War veterans, including both GWI cases and controls. This important study element was adopted to ensure that biological findings from the project would be identified in the most representative sample of Gulf War veterans possible. As outlined in the funded proposal, this involves identifying, contacting, and screening a random sample of Gulf War veterans currently living in the Central Texas target area. Developing such a sample required that we work with DOD's Defense Manpower Data Center (DMDC) to obtain names and contact information for Gulf War veterans whose last DOD address of record was in Central Texas. Due to delays in obtaining DMDC data, described below, we revised our approach in order to have the option of developing our study sample using alternate strategies.

Delays Associated with Defense Manpower Data Center (DMDC) Data Request

Since before our study proposal was submitted to CDMRP, we have worked with DMDC data management personnel on an ongoing basis to clarify the details and requirements of the data request we would submit in order to develop the study sample for the project. After obtaining HRPO approvals for the project in November, 2013, we formally submitted our data request to DMDC the first week of December, 2013, to obtain sampling information on 1991 Gulf War veterans residing in Central Texas. Our request was approved by the DMDC human subjects' office on December 6, and by the DMDC Survey Division on December 18, 2013. We were initially told that we could expect to receive the DMDC data set in January 2014, but were subsequently told that our request had been delayed. In March, 2014, we were informed that the DMDC Privacy Office would not authorize release of the requested data because Baylor did not maintain a data security system that was certified to meet federal IT security specifications (FISMA or corporate equivalent). This was unexpected, since no such requirements had been previously identified to us in putting together the project and data request. Nor had other CDMRP GWIRP research projects that had obtained DMDC data been required to meet these IT requirements. After discussions with multiple offices within DMDC and our CDMRP Program Officers, we were advised by DMDC that Baylor should establish or partner with an institution that has a federally credentialed IT system (e.g. FISMA, DIACAP) or a corporate equivalent (e.g. PCI).

After multiple leads and contacts with institutions across the region, we determined that there was no suitable IT-credentialed university or other research institution with which we could partner. We therefore worked with the Baylor IT security office and an identified corporate partner to establish a solution involving a PCI-certified system. When we informed the DMDC

Privacy Office that we had identified this option in May, 2014, we were told that no matter the level of security of the Baylor system, DMDC would not release data to a nonfederal entity. DMDC also indicated that they would only release the data to another federal entity after working out a Memorandum of Understanding (MOU) established for this purpose.

We learned from our CDMRP program office that CDMRP does not have the capability to arrange for an MOU of this nature. However, in helping to identify an alternate solution for obtaining DMDC data, CDMRP program officers conferred with the Research Facilitation Team (RFT) of the Army Analytics Group (AAG), who believed they could arrange for the required MOU and transfer of data. Beginning in late July, 2014, the PI of the current project worked with a representative of the RFT/AAG to discuss options and possible solutions for obtaining the necessary data to identify Gulf War veterans in Central Texas for the project. We learned in early September 2014, however, that the AAG did not believe they could provide a solution for obtaining the needed data. Dr. Lidie, our CDMRP Program Director, then contacted the RFT/AAG to ask that the matter be further considered. A conference call was held on September 22, 2014, that included officials and data management personnel from the RFT/AAG, the DMDC Privacy Office and data management representatives, Dr. Lidie, and the PI. The RFT/AAG team indicated they would move forward with a plan under which they would establish an MOU with DMDC to obtain the data and would work with us to provide the necessary documentation and assurances related to data management and security. Draft language for the MOU, including Baylor IT security documentation, was provided to the AAG RFT in March 2015. Subsequent communications with RFT personnel resulted in their developing the data sharing plan, which was presented to DMDC. We were informed on May 21, 2015, however, that after discussions with DMDC senior leadership, AAG determined that they could not assist with our data request. The Principal Investigator subsequently contacted DMDC senior leadership to request additional information re: requirements that would need to be met to obtain the requested DMDC data. No additional information has yet been provided.

Parallel to the data efforts involving the RFT/AAG, the PI of the project also worked to identify an alternate Army partner with the capability of arranging an MOU and obtaining the DMDC data. Although a capable and experienced Army data partner was identified, repeated attempts to obtain DOD or DMDC-specific guidelines for data security provisions to be followed by this partner for obtaining and sharing the DMDC data have not been successful. Attempts to work with this Army partner for obtaining DMDC data remain on hold, pending identification of the required guidelines.

Alternate Strategy for Sample Development and Recruitment

Due to the extended delays associated with obtaining DMDC data to develop the research sample for this project, we developed a backup plan to provide alternative options for recruiting veterans for the study. Although using a different sampling approach is expected to diminish the overall quality and replicability of the data obtained from the study, the extended delays involved in initiating data collection make this backup option necessary. We therefore reached out to VA officials and representatives of veterans' groups to lay the groundwork for implementing alternate study recruitment methods for the project, in the event a solution for obtaining sampling

information from DMDC could not be worked out. As detailed below, the revised plan includes two additional methods for recruiting veterans to serve as study subjects.

Alternate Recruitment Strategy 1: Recruitment of Veterans identified through VA's Gulf War Registry. The preferred alternate recruitment strategy involves access to veterans currently enrolled in the VA's Gulf War Registry. This includes all 1991 Gulf War veterans in the region who have come forward to enroll in VA's Gulf War Registry since their return from Desert Storm. Accessing veterans through the registry is preferred to other recruitment strategies, since the sample of veterans recruited in this way is more similar to a population-based sample, and more representative of Gulf War veterans overall, than veterans identified through other methods. We have been informed that at least 2,000 1991 Gulf War veterans are on VA's Central Texas Registry.

Alternate Recruitment Strategy 2: Media outreach, working with veterans' organizations, and scheduled events to alert area Gulf War veterans about our studies and invite their participation. Our second back-up recruitment option is to undertake a more conventional subject recruitment effort, working through our public affairs office and local media, as well as area veterans groups, national Gulf War veterans groups, and local chapters of national veterans service organizations (VSOs) to reach out to Gulf War veterans in Texas. We are prepared to use all of these methods to make contact with area Gulf War veterans, alert them to our research program, and invite their participation in the study. We already know that there are thousands of 1991 Gulf War veterans living in our target region (informed both by census information and the Gulf War Registry rolls). However, a study sample identified in this way is expected to be considerably less representative of Gulf War veterans, overall, than a population-based sample, so is likely to introduce a degree of bias into our study results.

Computer Assisted Telephone Interview (CATI) for Subject Screening and Recruitment
One additional activity outlined under Task 2 has been accomplished—preparation of the telephone interviewing software to be used in screening potential subjects for the project. Regardless of the methods ultimately used to identify the study sample, CATI screening is required to further characterize potential subjects to determine if they are eligible for the study and willing to participate. The specialized CATI software used for the project will provide interviewers with real time determinations of Gulf War illness case/control status, using a complex algorithm to assist in identifying individuals who are or are not eligible to participate in the study. CATI project directors and research staff have completed and tested CATI programming for the project. We will therefore be ready to move forward with screening of study subjects, once the sampling issues are resolved.

Because of the extended time allowed in our initial timeline to obtain OMB approvals for this study, it was expected that data collection would begin in the second year of the project. However, due to delays stemming from unanticipated regulatory issues, a necessary study site change, DMDC data acquisition, and institutional delays at our primary data collection sites, no subject recruitment or data collection activities have been initiated at this time.

Tasks 3 – 5.

No activities completed or underway at this time.

Project Timeline and Location

As previously described, extensive delays resulting from DOD's initial misdirection concerning OMB approvals, our inability to obtain DMDC data, and extended institutional delays at Baylor and collaborating institutions have caused considerable concerns regarding the timeline required for completing the project. We have concluded it is unlikely that the project can be completed in an acceptable timeframe under current circumstances. We therefore requested a 12 month extension without funds (EWOF) for the project on October 9, 2015. The PI also arranged to move her program to a different research institution that can provide enhanced research capabilities and resources. She recently accepted a new faculty position at Baylor College of Medicine (BCM) in Houston, Texas. Baylor University has agreed to return remaining grant funds for this project to DOD, so that they can be made available to BCM to complete the project there. Although we understand this change will bring additional project delays associated with the award transfer, we expect the enhanced resources and capabilities at BCM for FISMA-compliant IT management, MRI scanning, and clinical /laboratory evaluations will allow us to implement and complete project activities at an accelerated pace, without the need for clinical site subawards.

Key Research Accomplishments

Only regulatory submissions and planning for CATI interviews and clinical activities have been accomplished to date. Study data have not yet been collected.

Reportable Outcomes

There are no manuscripts or other reportable outcomes at this time.

Conclusion

No research results are yet available; no conclusions can be drawn at this time.

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